Dear Dr. Ferdinands,

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting with editors and our statistical consultant in attendance. We are interested in proceeding with the paper provided the minor comments of reviewers and editors can be addressed. Thank you for entrusting us with your work.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Sincerely,

Dr Elizabeth Loder

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**Report from The BMJ’s manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Report of the manuscript meeting of 14 July 2022

Present: Navjoyt Ladher (chair); Angie Wade (statistical editor); Nazrul Islam; Wim Weber; Di Wang; Tiago Villanueva; Elizabeth Loder

Decision: Request revisions before final acceptance

* Our statistical editor thought the reviews were excellent and did not have additional requests. She does note that there are points to address (including potential bias from influenza cases and selection bias, selection of covariates, correlations between controls included multiple times) but felt these were all addressable.
We've recently seen a paper that recommended against using hospitalised cases of Omicron as the outcome (https://www.sciencedirect.com/science/article/pii/S0264410X22005230). Could you address some of the matters raised in this paper in your discussion?

We would like to take you up on your offer to add additional information. It would be particularly useful if you are able to add information about the 4th dose.

Editors were generally impressed that this is well reported. We hope that this information might be persuasive to those in the US who have been hesitant to get boosters.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how and where you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1
Comments:
The authors applied the test-negative design to linked laboratory, vaccination, and health administrative databases to evaluate waning of 2-dose and 3-dose vaccine effectiveness of mRNA COVID-19 vaccines against hospitalizations and emergency department/urgent care visits for COVID illness in various subgroups (by age group, by immunocompromise, by vaccine product) during periods of Omicron, Delta, and pre-Delta variant predominance (from Jan 2021 to April 2022). This work leveraged the established CDC-funded VISION network of healthcare systems representing 10 US states to give them an adequately large sample size to evaluate the waning VE against moderate and severe outcomes under various circumstances.

I thought the authors used highly rigorous methods and interpreted their results appropriately, so I will not recount the many positives of this impressive work. I think the paper could be published essentially as is. I only have a few comments for the authors’ consideration that might further strengthen an already strong study.

1. In the Supplementary Figures, I noted that the outcomes don’t always correlate with SARS-CoV-2 test positivity for some of the sites (e.g., HealthPartners, Columbia University, Kaiser Permanente NorthWest), which I suspect reflects differences in geographical scope (i.e., a specific sub-state catchment area for the site’s outcome data vs. state-level SARS-CoV-2 testing data). I understand that the authors intended to adjust for the “7-day average SARS-CoV-2 test positivity in the area of the encounter” but how appropriate is it to use state-level SARS-CoV-2 test positivity given the inconsistent correlation (at least for some sites)? Would it be possible to use site-level (instead of state-level) SARS-CoV-2 positivity data instead? Perhaps I have misunderstood and that is what the authors actually used. If indeed that is the case, perhaps the figures could be revised to reflect that.

2. Since the authors specified periods of variant predominance based on when a variant account for 50% of sequenced isolates for each site, I wonder if a sensitivity analysis using a higher threshold (e.g., 90%) to specify periods of variant predominance would be worth considering. I understand that doing so will reduce precision, but may increase validity in the variant-specific estimates of VE.

3. A recent paper by Doll et al (https://pubmed.ncbi.nlm.nih.gov/35325923/) suggested that inclusion of influenza cases among test-negative controls can lead to downward bias of COVID-19 VE estimates due to correlated influenza and COVID-19 vaccination behaviours. I noted that the list of COVID-19-like illness conditions in Table S1 included a number of influenza-related diagnoses. What proportion of test-negative controls had an ICD-9/10 code for influenza, and did this vary over time such that this bias could have affected the apparent waning of COVID-19 VE observed in this study? Perhaps it biased all the estimates, but the impact of the bias would appear larger for VE estimates that are further from the null, leading to accentuation of the impact of waning.

Additional Questions:
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If you have any competing interests please declare them here: I conduct studies of influenza and COVID-19 vaccine effectiveness using similar methods, and have collaborated with some of the authors of this paper in the past.
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Reviewer: 2
Comments:
This peer review was conducted as a part of the Peer Review and Biomedical Editing Training Initiative (Peerspectives), which has been developed by the Institute of Public Health at the Charité - Universitätsmedizin Berlin in cooperation with the BMJ.

Summary:
This study investigates the waning of mRNA vaccine effectiveness against moderate (emergency department/urgent care clinic visit) and severe (hospital admission) COVID-19 in a test-negative design study. The authors have presented their study well. In particular, the authors address lots of important angles through appropriate subgroup analyses (i.e., age, immunocompromised status, type of mRNA vaccine) and sensitivity analyses. The authors find that effectiveness of mRNA vaccines wanes in the months following both second and third vaccination and conclude that these findings support current recommendations for broad use of additional vaccine doses. The major limitation of the paper is the potential for selection bias through the test-negative study design.

Importance:
The COVID-19 pandemic is ongoing, and this study adds to the body of work demonstrating the effectiveness of mRNA vaccines and the utility of “booster” vaccines, even more so for high-risk groups such as immunocompromised patients. This study will therefore directly contribute to COVID-19 vaccination policy decisions.

Originality:
As mentioned in the introduction and the discussion (p.11, ll. 283-289) of the manuscript, there is already evidence on vaccine effectiveness, and whether it wanes. This study replicates these findings in a large and multi-site cohort. The authors state the originality as assessing loss of effectiveness amongst all vaccine recipients while additionally performing subgroup analyses by age, immunocompromised status, and vaccine product. Whilst encouraging to see, the replication of findings from multiple studies does question the originality of the study.

Major comments:
1. General / Design: The test-negative study design poses a risk for selection bias (e.g., due to conditioning on having a test [see Li et al, Comparison of the test-negative design and the cohort design with explicit target trial emulation for evaluating Covid-19 vaccine effectiveness. SER Conference. June 14-17, 2022] and due to only including patients in the hospital/ED/UC setting). The least that the authors could do is to discuss this limitation. Ideally, a target trial design could be used for such a causal question (as done for example by Dickerman et al. [2022], [DOI: 10.1056/NEJMoa2115463]).

2. Introduction: The Introduction section could be a bit more elaborate, for example about the previous research done on this topic and a clearer description of the primary and secondary objectives. While we read the manuscript, we felt that “waning” relates to the difference in vaccine coverage, while the manuscript mainly focuses on unadjusted repeated vaccine effectiveness measurements.
3. It currently is also unclear why the authors only present and discuss the unadjusted vaccine effectiveness results in the main text (as well as in the abstract), while adjustment for different subgroups seems to be the main goal. Would it be possible to explain this and to provide information about the adjusted estimates as well?

4. Methods: Please discuss the selection of covariates (ideally with a DAG or similar) and why some potentially influential confounders are not captured by your study (e.g., BMI, certain occupations, etc.).

5. Results: The authors provide confidence intervals (CIs) for the estimates of VE, however, the primary focus of the paper is the level of waning estimated (the difference between VEs at different time points). These estimates of waning also need CIs (or another measure of uncertainty), otherwise the reader does not know how precise these estimates are, which is key to appropriately interpreting the level of waning.

6. Results: We suggest providing the CIs for every estimate of VE in the main body of the text (in addition to the tables).

7. Results: Would it please be possible to include forest plots for the adjusted VE analyses, too?

8. Discussion: we would have liked to see a discussion about the fact that the uncertainty around the estimates of VE is particularly large for younger age groups and immunocompromised (IC) individuals.

9. Please discuss the results of the sensitivity analysis including “negative control exposure” (p. 9, l. 269, VE: 8-23%) and provide results by age subgroups, too.

10. Please provide footnotes in the supplementary tables with information about which variables were adjusted for (they might be lacking due to a formatting issue).

11. Discussion section: Whilst we admire the translation of results into absolute numbers in the Discussion section, given the previous point, we wonder if the numbers presented are valid.

12. Please give more reasoning on the statement in the discussion that you consider the waning “clinically significant” (p. 11, l. 325), as the final outcomes of the patients remain unclear. We suggest maybe not referring to this as “clinically significant”.

Minor Comments:
1. We would suggest relating the percentages in Table 1 to the respective total number of participants in each column (e.g., SARS-CoV-2 Negatives in January 2021 divided by total number of SARS-CoV-2 Negatives). This would enable easier comparison of characteristics between groups.

2. It should furthermore be discussed that the geographic areas that were “adjusted” for were quite large considering the authors’ goal to establish comparability. A full adjustment for the waning of vaccine-induced immunity might therefore not have been possible. So, we suggest removing “clearly” from line 295 on page 10.

3. We wonder why it is stated on p. 7 l. 193 that p values < 0.05 were considered statistically significant, while no p values are included thereafter or referenced to. Maybe this addition is not needed.

4. P. 5, l. 159: Ideally, please describe the rationale behind the choice of (a) categorising the time variable, (b) 2-months, and (c) the choice of subgroup categories (e.g., age groups) (p. 7, l. 182)?

5. We have concerns about potential correlations between controls, as they could participate in the study multiple times (p. 5, l. 147, 148) and would ideally like to see this discussed.

6. Could you provide some rationale why your focus was on mRNA vaccines?

7. If the authors can find space: to further align the abstract with the main text, suggest including 'with a focus on three-dose protection against severe disease during Omicron period' in the objectives, as set out in the introduction. Especially as this is one of the unique features of the study.

8. We would have preferred a flow chart (STROBE statement 13c) to show the disposition of study participants over the description of included and excluded participants in Tables S7 and S8.
9. If sample size permits, we suggest presenting the same time intervals for the IC subgroup as for the non-IC subgroup in the Figure with the forest plots for better comparability (p. 24).
10. Please state explicitly that the data was collected retrospectively.
11. In some tables (e.g., S9 and S10) there are green triangles in the upper left corner of a subset of cells, which need to be removed.
12. It could be discussed as a limitation that the final clinical outcomes remain unclear (p. 10, l. 291]).

COI STATEMENT:
This peer review was done under the Peer Review and Biomedical Editing Training Initiative (Peerspectives), which has been developed in cooperation with the BMJ. In total, 2 PhD students from Charité - Universitätsmedizin Berlin, one PhD from University Cologne and MSc Epidemiology student (Charité - Universitätsmedizin Berlin), one PhD student from the University of Leicester UK, and one experienced mentor reviewed this paper. All participants have agreed to the BMJ reviewer policies.

PhD Students:
1 Vanessa Voelskow
2 Clareece Nevill
3 Richard M. Köhler
4 Nora Tabea Sibert

Mentor (takes responsibility for the review):
Mariska Leeflang

Potential competing interests:
ML, VV, RMK, CN and NTS have nothing to declare.

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